



Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all transgender people with HIV to improve their health and to reduce the risk of HIV transmission to sexual partners **(AI)**.
- HIV care services should be provided within a gender-affirmative care model to reduce potential barriers to ART adherence and maximize the likelihood of achieving sustained viral suppression **(AII)**.
- Prior to ART initiation, a pregnancy test should be performed for transgender individuals of childbearing potential **(AIII)**.
- Some antiretroviral (ARV) drugs may have pharmacokinetic interactions with gender-affirming hormone therapy. Clinical effects and hormone levels should be monitored routinely with appropriate titrations of estradiol, testosterone, or androgen blockers, as needed **(AIII)**.
- Gender-affirming hormone therapies are associated with hyperlipidemia, elevated cardiovascular risk, and osteopenia; therefore, clinicians should choose an ART regimen that will not increase the risk of these adverse effects **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Introduction

Because transgender and nonbinary people bear a disproportionate burden of HIV, it is important for HIV care providers to be knowledgeable about the specific HIV care needs of these individuals.

Terminology

Transgender people are broadly defined as those whose gender identity differs from their assigned sex at birth.^{1,2} The terminology used to define transgender identities continues to evolve over time and across geographical and cultural contexts.³ The terms cisgender, cis-man, and cis-woman are used to describe persons who identify with their assigned sex at birth. The terms used to describe women who were assigned male at birth include transgender women, trans women, transfeminine individuals, and women of transgender experience. The terms for men who were assigned female at birth include transgender men, trans men, transmasculine individuals, and men of transgender experience. Some individuals identify outside the gender binary of man or woman, using words such as gender nonbinary, genderqueer, and gender nonconforming to describe themselves. Other individuals may not have a fixed sense of their gender and may move back and forth among different gender identities; these individuals are described as gender fluid. Gender persons do not identify with having any gender and can use other terms such as null-gender or neutrois.

Gender affirmation describes processes whereby a person receives social recognition, value, and support for their gender identity and expression.⁴ Gender affirmation is often described across several dimensions, including social (e.g., social support and acceptance, use of pronouns, names, or clothing that align with their gender identity), medical (e.g., use of hormones or surgery), legal (e.g., legal name change or changing gender markers on identity documents), and psychological (e.g., the degree of self-acceptance and comfort with their gender identity).⁵ Medical gender affirmation has been shown to improve mental health outcomes and measures of well-being in transgender individuals.^{6,7}

Epidemiology

National surveys indicate that 1.4 million adults in the United States aged 18 years and older identify as transgender, representing 0.6% of the adult population.⁸ It is estimated that almost 2% of high school students identify as transgender.^{9,10} National, population-based estimates of the numbers of gender nonbinary people in the United States are not yet available; however, 31% of the 27,715 people who completed the 2015 U.S. Transgender Survey (USTS) identified as gender nonbinary.¹¹ Meta-regression modeling suggests that the number of people who are willing to report that they are transgender and/or gender nonbinary is

likely to increase in the future.¹²

The most recent estimate of HIV prevalence among transgender people is 14% among transgender women and 2% among transgender men.¹³ The highest prevalence is among black (44%) and Hispanic/Latino (26%) transgender women.¹³ Not enough data were available to estimate HIV prevalence by race/ethnicity among transgender men. Data on HIV prevalence among nonbinary individuals is scant. Of the nonbinary individuals who completed the 2015 USTS, 0.4% self-reported having HIV, including 1% of participants who were assigned male at birth and 0.2% of participants who were assigned female at birth.¹¹

In the first national-level analysis of transgender people with HIV, the National HIV Surveillance system identified 2,351 transgender people with newly diagnosed HIV infection from 2009 to 2014. Eighty-four percent of these individuals were transgender women, 15% were transgender men, and 0.7% reported other gender identities.¹⁴ More than one-half of both transgender women (51%) and men (58%) with newly diagnosed HIV were black/African American. Most of these individuals were aged 25 years to 34 years (35%) or 20 years to 24 years (26%). Almost one-half of transgender people with newly diagnosed HIV resided in the South (44%), and 18% had AIDS at the time of diagnosis.

In 2017, the Ryan White HIV/AIDS Program provided services for 8,811 transgender people, representing 1.8% of Ryan White clients.¹⁵ Of these transgender clients, 7,837 (89%) were transgender women, 853 (10%) were transgender men, and 121 (1%) were transgender with current gender unknown. The majority were black and/or African American (5,081 individuals [57.6%]) or Hispanic/Latino (2,619 individuals [29.7%]).

HIV Care Continuum

Some studies have reported that transgender women living with HIV are less likely than cisgender men to receive antiretroviral therapy (ART), be adherent to ART, and achieve viral suppression.¹⁶⁻²¹ Transgender people may experience numerous barriers to successful engagement along the HIV care continuum.^{11,22} For example, compared with Ryan White clients overall, transgender clients were significantly less likely to have stable housing (77% vs. 87%), live above the federal poverty level (24% v. 37%), and be virally suppressed (81% v. 86%).¹⁵ Experiences of violence, discrimination, and other trauma¹¹ are common among transgender people and have been associated with ART failure.²³

Barriers to HIV Care and Treatment

Transgender people may avoid the health care system due to stigma and past negative experiences (e.g., being called the wrong name or pronoun, being verbally harassed, asked invasive questions about being transgender, or having to educate their providers about transgender people).^{11,13,14,24-26}

For many transgender people, gender-affirming therapy (e.g., feminizing hormones) is a greater priority than HIV treatment and care.^{27,28}

Concerns about adverse interactions between antiretroviral (ARV) drugs and gender-affirming hormone therapy are common among transgender people.²⁷ One study found that 40% of transgender women with HIV did not take their ARV drugs as directed due to concerns about drug-drug interactions, yet less than half had discussed this concern with their providers.²⁹

Facilitating HIV Care Engagement

Gender Affirmation

Individuals are more likely to engage in HIV care when gender affirmation needs are met.^{4,25} A national study of transgender people with HIV found that participants who work with HIV care providers who affirm their gender (e.g., who use their chosen name and pronoun) were more likely to be virally suppressed.²⁸ Adherence to hormone therapy correlates with adherence to ART.^{30,31} However, making access to hormone therapy contingent upon ART adherence is associated with lower likelihood of viral suppression.²⁸

Integration of HIV Care with Gender Care

According to research with transgender youth²⁵ and adults,²⁷ integrating HIV care with gender care facilitates treatment and is associated with viral suppression. In addition to minimizing the number of provider visits and potentially stressful clinical interactions, care integration makes it easier to discuss concerns about drug-drug interactions between HIV treatment and gender-affirming medications. In instances where integrated care is not feasible, the ART prescriber should refer the patient to an appropriate hormone therapy prescriber. Collaboration between these two care providers may enhance the quality of care.

Peer Navigation

Peer navigation has been found to improve the likelihood of durable viral suppression among key populations, including transgender women.³² Research with youth and adults suggests that having visible transgender staff in the clinical environment also facilitates engagement in care.²⁵

Gender-Affirming Clinical Settings

Providing HIV services within gender-affirming environments should be a priority. Concrete steps that clinicians can take include ensuring that registration forms and electronic medical records are inclusive of transgender and gender nonbinary identities, preferably using a two-step method that records both gender and sex assigned at birth.³³ Individuals should be asked for their chosen name and pronouns, and these should be used consistently when speaking to or about the person, regardless of legal name. Clinicians and staff should avail themselves of resource lists, brochures, and other [materials](#) that meet the specific needs of transgender people living with HIV. Integrating hormone therapy with HIV services is the recommended practice and requires that HIV providers become knowledgeable about hormone therapy and other aspects of gender-affirming services. When integration of HIV and transgender services is not possible, patients should be referred to clinicians who are knowledgeable in the field of transgender medicine. Both the [World Professional Association for Transgender Health](#) (WPATH) and [GLMA: Health Professionals Advancing LGBTQ Equality](#) (previously known as the Gay & Lesbian Medical Association) have provider directories that list endocrinologists, primary care providers, and psychiatrists with expertise working with transgender populations.

Pharmacological Considerations

Hormone Therapy

Hormone therapy is an important aspect of gender-affirming care for many transgender individuals. Hormones facilitate the acquisition of secondary sex characteristics that are associated with the affirmed gender. Several guidelines for hormonal treatment of transgender people have been published, including guidelines from the [Endocrine Society](#)³⁴ and [WPATH](#).³⁵ Clinical outcomes, potential adverse effects, the patient's treatment goals, and the patient's current hormone levels should be taken into account when determining the appropriate doses of hormone and androgen blockers. A clinician should be aware of the typical doses and routes of administration for all of the hormones and androgen blockers that a patient is taking, whether these medications are prescribed or not. All additional interventions (such as gonadectomy) should be documented. These interventions could potentially increase the risk of ART-related adverse effects on cardiovascular and bone health.

Feminizing regimens that are used by transgender women and others who were assigned male at birth usually include estrogens and androgen blockers. Feminizing regimens result in breast growth, redistribution of body fat, softening of the skin, and a decrease in muscle mass.³² These regimens do not reduce facial (beard) hair or change the voice. In the United States, oral, parenteral, or transdermal preparations of 17-beta estradiol, or, less often, conjugated estrogens, are the mainstay of gender-affirming medical care for transgender women. Spironolactone, a mineralocorticoid receptor antagonist with anti-androgen properties, is usually used for androgen blockade; alternatives include 5-alpha reductase inhibitors that decrease the production of dihydrotestosterone (e.g., finasteride or dutasteride) or gonadotropin releasing hormone agonists (e.g., goserelin acetate and leuprolide acetate). Cyproterone acetate is a steroidal anti-androgen that is frequently

used outside of the United States. Patients may request progesterone to assist with breast growth; however, this has not been proven to be effective.³³ When using feminizing regimens, the goal is to suppress the testosterone level to <50 ng/dL and reach a serum estradiol level in the physiologic cisgender female range of 100 pg/mL to 200 pg/mL.³⁴

Masculinizing regimens for transgender men and others who were assigned female at birth involve parenteral or transdermal testosterone preparations. These regimens are designed to stimulate the growth of facial and body hair, increase muscle mass, and deepen the voice; use of these regimens also results in clitoral enlargement, vaginal atrophy, and amenorrhea.³⁴ When using masculinizing therapy, the testosterone levels should be kept in the usual cisgender male range of 400 ng/dL to 700 ng/dL.³⁴

Hormones and Antiretroviral Therapy

Studies that have examined interactions between exogenous estrogens and ART have predominantly focused on combined oral contraceptive use in cisgender women.³⁶ The data from these studies have been used to make predictions about the direction and extent of drug-drug interactions (Table 14). However, there are known differences between the pharmacologic characteristics of ethinyl estradiol, which is used in contraceptives, and 17-beta estradiol, which is used for gender affirmation. These differences may influence the accuracy of these predictions for feminizing hormonal regimens.

Table 14. Potential Interactions Between the Drugs Used in Gender-Affirming Hormone Therapy and Antiretroviral Drugs (page 1 of 2)

Potential Effect on GAHT Drugs	ARV Drugs	GAHT Drugs that may be Affected by ARV Drugs	Clinical Recommendations for GAHT
ARV Drugs with the Least Potential to Impact GAHT Drugs	All NRTIs <u>Entry Inhibitors:</u> • IBA • MVC • T-20 <u>Unboosted INSTIs:</u> • BIC • DTG • RAL <u>NNRTIs:</u> • RPV • DOR	None	No dose adjustments necessary. Titrate dose based on desired clinical effects and hormone concentrations.
ARV Drugs that may Increase Concentrations of Some GAHT Drugs	EVG/c All boosted PIs	Dutasteride Finasteride Testosterone	Monitor patient for associated adverse effects; decrease the doses of GAHT drugs as needed to achieve the desired clinical effects and hormone concentrations.
ARV Drugs that may Decrease Concentrations of GAHT Drugs	PI/r <u>NNRTIs:</u> • EFV • ETR • NVP	Estradiol	Increase the dose of estradiol as needed to achieve the desired clinical effects and hormone concentrations.
	<u>NNRTIs:</u> • EFV • ETR • NVP	Dutasteride Finasteride Testosterone	Increase the doses of GAHT drugs as needed to achieve the desired clinical effects and hormone concentrations.

Table 14. Potential Interactions Between the Drugs Used in Gender-Affirming Hormone Therapy and Antiretroviral Drugs (page 2 of 2)

Potential Effect on GAHT Drugs	ARV Drugs	GAHT Drugs that may be Affected by ARV Drugs	Clinical Recommendations for GAHT
ARV Drugs with an Unclear Effect on GAHT Drugs	EVG/c PI/c	Estradiol	There is the potential for increased or decreased estradiol concentrations. Adjust the dose of estradiol to achieve the desired clinical effects and hormone concentrations.

Note: See Tables [21a](#), [21b](#), [21c](#), [21d](#), and [21e](#) for additional information regarding drug-drug interactions between ARV drugs and gender-affirming medications.

Key: ARV = antiretroviral; BIC = bictegravir; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; GAHT = gender-affirming hormone therapy; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; T-20 = enfuvirtide

Other Hormonal Therapy Considerations

Bone Health

Bone metabolism is influenced by sex hormones. Current recommendations for osteoporosis screening are based on age and sex and have not been studied in transgender populations, which include people who have used hormone therapy and/or undergone removal of their gonads. Studies investigating bone mineral density changes in transgender women have shown inconsistent results, with estrogens being associated with both elevations and declines in bone mineral density.³⁷⁻³⁹ In one study, transgender women had high rates of osteopenia even before initiating hormones, possibly due to low levels of physical activity and low vitamin D levels.³⁷ Transgender men who are receiving testosterone appear to maintain adequate bone mineral density.⁴⁰ The risk for osteoporosis increases after gonadectomy, especially if hormone regimens are stopped. Consequently, clinicians should consider early screening in this setting.

When using the FRAX[®] tool, which requires a sex designation, expert consensus is that assigned birth sex should be used, since transgender people who initiate hormones in early adulthood have generally already achieved peak bone mass.⁴¹ Transgender people with HIV should be screened for osteoporosis using dual energy X-ray absorptiometry by age 50, in accordance with current primary care recommendations.⁴²

Since the use of tenofovir disoproxil fumarate (TDF) has been associated with reductions in bone mineral density in people with HIV, TDF should be used with caution in transgender people with risk factors for osteoporosis or in those with established osteoporosis.

Interpretation of Laboratory Values

Interpretation of laboratory results requires special attention when reference ranges vary by sex. The sex listed on laboratory requisition forms typically corresponds with the gender listed on the patient's insurance forms and may not reflect the patient's current anatomical or hormonal configuration. Normal values have not been established for transgender individuals who are receiving gender-affirming hormonal or surgical interventions. Interpretation of laboratory results is dependent on the patient's physiology and the specific test being performed. Feldman et al.⁴³ recommend the following:

- For transgender people who are not taking hormones and have not had gonadectomy, use the sex assigned at birth.
- For transgender people who have undergone gonadectomy and have been stable on hormone therapy, use their affirmed gender.

- For transgender people who retain natal gonads and who may have been on hormone therapy for shorter periods of time, some laboratory tests may require the use of male reference ranges, while others may require the use of female reference ranges.
- Guidelines from the Center of Excellence for Transgender Health¹ recommend using the limits of normal described in the table below.

Limits of Normal When Interpreting Selected Laboratory Results in Transgender Adults

Laboratory Measures	Transgender Women on Gender-Affirming Hormones		Transgender Men on Gender-Affirming Hormones	
	Lower Limit	Upper Limit	Lower Limit	Upper Limit
Alkaline Phosphatase	Not defined	Male value	Not defined	Male value
Creatinine	Not defined	Male value	Not defined	Male value
Hemoglobin/Hematocrit	Female value	Male value	Male value ^a	Male value

^a If the patient is menstruating regularly, consider using the female lower limit of normal.

Providers are encouraged to consult with their local laboratories to obtain hormone level reference ranges for both ‘male’ and ‘female’ norms, and then apply the correct range when interpreting results based on the current hormonal sex, rather than the sex on the laboratory form.¹ Reference intervals for transgender people have not been established; therefore, hormone status and clinical judgment must be used to assess abnormal laboratory values.⁴⁴

Renal Concerns

Gender-affirming hormones can affect estimates of glomerular filtration rates (eGFR) that rely on serum creatinine due to changes in muscle mass. In one study, transgender men on testosterone had a mean increase in levels of serum creatinine from 0.73 ± 0.03 mg/dL to 0.87 ± 0.04 mg/dL after 3 months to 6 months of treatment. Transgender women on estrogen had a decrease in mean serum creatinine levels from 0.90 ± 0.03 mg/dL to 0.85 ± 0.03 mg/dL.⁴⁵ Creatinine-based eGFR calculations may therefore overestimate GFR in transgender women or underestimate GFR in transgender men on hormones. Therefore, using [cystatin C-based eGFR calculations](#) may be preferred for patients with marginal renal function.

Cardiovascular Disease Risk

Transgender individuals may have elevated cardiovascular disease (CVD) risk, due to both traditional risk factors and the risk factors associated with hormone use. Rates of tobacco use are higher among transgender people than in the general population,⁴⁶ and transgender women have a higher risk of venous thromboembolism and ischemic stroke, primarily associated with duration of estrogen use.⁴⁷ Transgender women on estrogens may show an increase in serum levels of triglycerides and high-density lipoproteins (HDL), with a decrease in levels of low-density lipoproteins (LDL).⁴⁸ Exogenous testosterone has been associated with increased levels of LDL and decreased levels of HDL among transgender men.⁴⁸ Providers should take into consideration CVD risk when selecting ART regimens and gender-affirming hormone therapy regimens.

Assessment of cardiac risk among transgender people with HIV can be complicated by hormone-induced changes in lipid levels as well as sex-specific variations in homocysteine and high sensitivity C-reactive protein.⁴⁹ American Heart Association guidelines recommend using sex-specific calculators to determine cardiovascular risk and guide interventions,⁵⁰ and they provide no guidance for transgender people whose assigned sex at birth may differ from their hormonal and/or anatomical sex. The Center of Excellence for Transgender Health recommends that providers use the risk calculator for the sex at birth, affirmed gender, or an average of the two depending on the age at which the patient began using hormones and the total amount of time that a patient has been on hormone therapy.¹

For transgender people with an elevated CVD risk or a history of CVD events, ARV drugs that are associated with CVD should be avoided whenever possible. See [Table 17](#) for a list of ARV drugs that are associated with an increased risk of CVD. See [Table 18](#) for alternative ARV agents to use in individuals with CVD. In transgender women who have an elevated risk for CVD or who have experienced a CVD event, transdermal estradiol may be the safest option for hormone therapy, as it carries a lower risk of thromboembolism than other routes of administration.⁵¹

Pregnancy Potential

Important information on contraception, drug-drug interactions between ARV drugs and hormonal therapy drugs, and pregnancy is provided in the [Women with HIV](#) section. Much of this information also applies to transgender and nonbinary individuals. Below are specific ART considerations for transgender and nonbinary people with pregnancy potential. Clinicians who care for pregnant patients should also consult the current [Perinatal Guidelines](#) for a more in-depth discussion and guidance on managing these patients.

Some transgender individuals use exogenous hormones and/or undergo gonadectomy for gender affirmation. Understanding exactly what interventions someone has undergone and the timeline for these interventions will clarify the patient's potential for pregnancy. Transgender individuals without a uterus (by birth or by hysterectomy) do not have pregnancy potential. For transgender people who retain a uterus and ovaries, ovulation may continue in the presence of hormone therapy, and fertility is possible.¹ Gender-affirming surgeries do not impair fertility unless the uterus, ovaries, and vagina are removed.^{52,53} All transgender people who have a uterus and ovaries and engage in sexual activity that could result in pregnancy should receive a pregnancy test prior to initiating ART (**AIII**). All ART-naïve persons who are pregnant should be started on ART for their health and to prevent transmission of HIV to the fetus. They should be counseled about ARV drug use during pregnancy, and clinicians should consult the [Perinatal Guidelines](#) when designing a regimen (**AIII**). Unless there are no alternative options, dolutegravir **should not be prescribed** for individuals who are pregnant and within 12 weeks post-conception; who are of childbearing potential, sexually active, and not using effective contraception; or who are contemplating pregnancy (**AII**).

Testosterone Exposure in Transgender Persons with Ovaries

Testosterone alone is not a reliable form of contraception, and pregnancies have been reported in transgender men following prolonged testosterone treatment. Testosterone is a teratogen, and it is contraindicated in pregnancy. Clinicians should assess the reproductive desires and fertility potential of their transgender patients and provide accurate information on contraceptive and reproductive options.⁵⁴

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